Effectiveness of pharmacological treatments for COVID-19 due to SARS-CoV-2: a systematic literature review

SUPPLEMENTS

SUPPLEMENT 1A. PUBMED SEARCH STRATEGY

ARBIDOL

Search: arbidol covid-19 Filters: Meta-Analysis Sort by: Most Recent (("umifenovir"[Supplementary Concept] OR "umifenovir"[All Fields] OR "arbidol"[All Fields] OR "arbidole"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))) AND (meta-analysis[Filter])

FAVIPIRAVIR

Search: favipiravir covid 19 Filters: Meta-Analysis Sort by: Most Recent (("favipiravir"[Supplementary Concept] OR "favipiravir"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))) AND (meta-analysis[Filter])

HIDROXICLOROQUINA-CLOROQUINA

Search: hydroxychloroquine covid-19 Filters: Meta-Analysis Sort by: Most Recent (("hydroxychloroquine"[MeSH Terms] OR "hydroxychloroquine"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))) AND (meta-analysis[Filter])

INTERFERON

Search: interferon covid 19 Filters: Meta-Analysis Sort by: Most Recent (("interferon s"[All Fields] OR "interferone"[All Fields] OR "interferones"[All Fields] OR "interferons"[MeSH Terms] OR "interferons"[All Fields] OR "interferon"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))) AND (meta-analysis[Filter])

LOPINAVIR-RITONAVIR

Search: lopinavir ritonavir covid-19 Filters: Meta-Analysis Sort by: Most Recent (("lopinavir"[MeSH Terms] OR "lopinavir"[All Fields]) AND ("ritonavir"[MeSH Terms] OR "ritonavir"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))) AND (meta-analysis[Filter])

REMDESIVIR

Search: remdesivir covid 19 Filters: Meta-Analysis Sort by: Most Recent (("remdesivir"[Supplementary Concept] OR "remdesivir"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))) AND (meta-analysis[Filter])

SARILUMAB

Search: sarilumab covid 19 Filters: Meta-Analysis Sort by: Most Recent (("sarilumab"[Supplementary Concept] OR "sarilumab"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR

"covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))) AND (meta-analysis[Filter])

TOCILIZUMAB

Search: tocilizumab covid 19 Filters: Meta-Analysis Sort by: Most Recent (("tocilizumab"[Supplementary Concept] OR "tocilizumab"[All Fields]) AND ("covid 19"[All Fields] OR "covid 19"[MeSH Terms] OR "covid 19 vaccines"[All Fields] OR "covid 19 vaccines"[MeSH Terms] OR "covid 19 serotherapy"[All Fields] OR "covid 19 nucleic acid testing"[All Fields] OR "covid 19 nucleic acid testing"[MeSH Terms] OR "covid 19 serological testing"[All Fields] OR "covid 19 serological testing"[MeSH Terms] OR "covid 19 testing"[All Fields] OR "covid 19 testing"[MeSH Terms] OR "sars cov 2"[All Fields] OR "sars cov 2"[MeSH Terms] OR "severe acute respiratory syndrome coronavirus 2"[All Fields] OR "ncov"[All Fields] OR "2019 ncov"[All Fields] OR (("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "cov"[All Fields]) AND 2019/11/01:3000/12/31[Date - Publication]))) AND (meta-analysis[Filter])

WITHOUT RESULTS (strategies with the same structure)

APN01
CAMRELIZUMAB
DANOPREVIR
DARUNAVIR-COLICISTAT
ECULIZUMAB
LERONLIMAB
REGN 3048
TIMOSINA ALFA 1 (TIMALFASINA)

SUPPLEMENT 1B. COCHRANE LIBRARY STRATEGY (https://www.cochranelibrary.com/)

Search: ARBIDOL, FAVIPIRAVIR, HIDROXICLOROQUINA-CLOROQUINA, INTERFERON, LOPINAVIR-RITONAVIR, REMDESIVIR, SARILUMAB, TOCILIZUMAB, APN01, CAMRELIZUMAB, DANOPREVIR, DARUNAVIR-COLOSTAT, ECULIZUMAB, LERONLIMAB, REGN 3048, TIMISINA ALFA 1 (TIMALFASINA).

SUPPLEMENT 1C. EUROPEAN MEDICINES AGENCY (https://www.ema.europa.eu/en/medicines)

Search: ARBIDOL, FAVIPIRAVIR, HIDROXICLOROQUINA-CLOROQUINA, INTERFERON, LOPINAVIR-RITONAVIR, REMDESIVIR, SARILUMAB, TOCILIZUMAB, APN01, CAMRELIZUMAB, DANOPREVIR, DARUNAVIR-COLOSTAT, ECULIZUMAB, LERONLIMAB, REGN 3048, TIMISINA ALFA 1 (TIMALFASINA).

SUPPLEMENT 1D. AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS (https://www.aemps.gob.es/)

Search: ARBIDOL, FAVIPIRAVIR, HIDROXICLOROQUINA-CLOROQUINA, INTERFERON, LOPINAVIR-RITONAVIR, REMDESIVIR, SARILUMAB, TOCILIZUMAB, APN01, CAMRELIZUMAB, DANOPREVIR, DARUNAVIR-COLOSTAT, ECULIZUMAB, LERONLIMAB, REGN 3048, TIMISINA ALFA 1 (TIMALFASINA).

SUPPLEMENT 1E. GOOGLE (https://www.google.com/)

Search: ARBIDOL, FAVIPIRAVIR, HIDROXICLOROQUINA-CLOROQUINA, INTERFERON, LOPINAVIR-RITONAVIR, REMDESIVIR, SARILUMAB, TOCILIZUMAB, APN01, CAMRELIZUMAB, DANOPREVIR, DARUNAVIR-COLOSTAT, ECULIZUMAB, LERONLIMAB, REGN 3048, TIMISINA ALFA 1 (TIMALFASINA).

Searches in COCHRANE LIBRARY, EUROPEAN MEDICINES AGENCY, AGENCIA ESPAÑOLA DE MEDICAMENTOS Y PRODUCTOS SANITARIOS and GOOGLE, were performed individually for each drug with the corresponding name, identifying - where appropriate - the corresponding meta-analyses.

SUPPLEMENT 2. ARTICLES INCLUDED IN THE SYNTHESIS (alphabetical order)

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SUPPLEMENT 5. SUPPLEMENTARY TABLES

Table S1. Interleukin 1 (IL-1) inhibitors: Anakinra. Meta-analysis of its effectiveness in the treatment of COVID-19.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2020	Kim	NMA	PRISMA	High	Observational	Standard treatment	Mortality Severe disease progression	1	NA	0.30 (0.11-0.82;0.019) 0.22 (0.09-0.56;0.002)	NA NA	M: 0.664 L: 0.835
2021	Barkas	REM/ FEM	PRISMA	High	RCT	Standard treatment	Mortality Admission to ICU with MV	9	485	0.32 (0.23-0.45;<0.00001) 0.38 (0.17-0.85;0.02)	LOW: 0% MED: 67%	M: 0.628 M: 0.533
2021	Khan	REM	PRISMA	High	Cohorts¶ Retrospectives	Standard treatment	Mortality	4 3	196 29	0.24 (0.07-0.79; ND) 0.70 (0.31-1.58;0.226)	NA LOW: 32.8%	M: 0.787 No association
2021	Pasin	REM/ FEM	PRISMA	High	Cohorts¶	Standard treatment	Mortality Admission to ICU with MV	4	111	0.26 (0.14-0.48;0.0001) 0.45 (0.25-0.82;0.008)	LOW: 0% LOW: 19%	M: 0.743 S: 0.440
2022	Peng	REM	PRISMA	High	Case-control	Standard treatment	Mortality 2nd infection risk	3	85	0.41 (0.19-0.85;0.017) 1.44 (0.47-4.43;0.520)	MED: 27.6% NA	S: 0.492 No association
2021	Putman	REM	PRISMA	High	Cohorts¶	Standard treatment	Mortality	2	60	0.25 (0.12-0.52;0.0002)	LOW: 0%	M: 0.764
2023	Shang	REM/ FEM	PRISMA	High	RCT	Standard treatment/PBO	Mortality (90 days)	5	941	1.01 (0.73-1.39;0.97)	LOW: 55%	No association

*The following criteria were used: (i) up to 25%, low heterogeneity (LOW); (ii) between > 25% and < 75%, moderate heterogeneity (MED); and, finally, (iii) if ≥ 75%, high heterogeneity (HIGH) (*Higgins, 2003*); ** By convention, for Cohen's "d" of 0-0.4; 0.5-0.7 and ≥ 0.8 are considered small (S), medium (M) and large (L) effect sizes respectively (*Chen, 2010*). Cohen's d was calculated using the tool available at the following URL: https://www.escal.site/. § References: PRISMA: *Liberati, 2009; Moher, 2009; Page, 2021; Cochrane: Cochrane, 2022; WHO: Shankar-Hari, 2021*. # Reference: *National, 2023*; ¶ Non randomized prospective cohort studies. Abbreviations: 95% CI: 95% confidence interval; FEM: fixed effects model; HIGH: high heterogeneity; HR: hazard ratio; L: large effect; LOW: low heterogeneity; M: medium effect; MED: average heterogeneity; MV: mechanical ventilation; NHLBI: National Heart, Lung and Blood Institute (*National, 2023*); NA: not available; NMA: network meta-analysis; OR: odds ratio; p: statistical significance; PBO: placebo; RCT: randomized clinical trials; REM: random effects model; RR: relative risk; S: small effect.

Table S2. Interleukin 6 (IL-6) inhibitors: Tocilizumab. Meta-analysis of its effectiveness in the treatment of COVID-19.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2020	Aziz	REM	PRISMA	High	RCT Cohorts	Standard treatment	Mortality MV need	23	1897	Risk difference: -0.06 (-0.12; --0.01;0.03) -0.11 (-0.19; -0.02;0.01)	 HIGH: 80.9% MED: 74.0%	-
2020	Berardicurti	REM	PRISMA	High	Prospectives Retrospectives	Standard treatment	Mortality	22	1520	0.47 (0.22-0.98;0.04)	MED: 68%	S: 0.416
2020	Lan	REM/ FEM	PRISMA	High	Retrospectives	Standard treatment /PBO	Mortality ICU admission risk	7	240	0.62 (0.31-1.22; NA)	MED: 68%	No association
2021	Alkofide	REM	PRISMA	High	RCT Retrospectives	Standard treatment	Mortality	17	727	0.58 (0.42-0.81; NA)	MED: 71%	S: 0.300
2021	Chen	REM/ FEM	Cochrane	High	RCT Cohorts	NA	Mortality ICU admission MV Secondary infection	30 7 13 10	2651 663 705 1201	0.74 (0.59-0.93; NA) 1.40 (0.64-3.06; NA) 0.83 (0.57-1.22; NA) 1.30 (0.97-1.74; NA)	HIGH: 80% HIGH: 88% MED: 65% MED: 65%	S: 0.166 No association No association No association
2021	Ghosn	REM	Cochrane	High	RCT	Standard treatment /PBO	Mortality day 28 Hospital discharge	8 7	3298 1764	0.89 (0.82-0.97; NA) 1.06 (1.00-1.13; NA)	LOW: 0% MED: 40.9%	S: 0.064 No association
2021	Khan	REM	PRISMA	High	Prospectives Retrospectives	Standard treatment	Mortality	20 40	6563	0.83 (0.72-0.96; NA) 0.52 (0.41-0.66; NA)	LOW: 0% HIGH: 76.6%	S: 0.103 S: 0.361
2021	Kyriakopoulos	REM	Cochrane	High	Observational RCT	Standard treatment	Mortality MV Mortality MV	38 10 9 4	4456 717 3358 2568	0.69 (0.58-0.83; NA) 0.81 (0.57-1.14; NA) 0.89 (0.82-0.96; NA) 0.81 (0.71-0.93; NA)	HIGH: 84% HIGH: 70.2% LOW: 0.3% LOW: 0%	S: 0.205 No association S: 0.064 S: 0.116
2021	Lin	REM	PRISMA Cochrane WHO	High	RCT	Standard treatment /PBO	Mortality Clinical improvement	8	3267	0.92 (0.66-1.28; NA)	MED: 62%	No association
2021	Moosazadeh	REM	Cochrane	High	RCT, Cohorts Tocilizumab + corticosteroids	Standard treatment /PBO	Mortality VS Tocilizumab Mortality VS Placebo	5 5	460 567	0.74 (0.36-1.50; NA) 0.48 (0.31-0.74; NA)	MED: 72.5% MED: 68.8%	No association S: 0.405
2021	Pinzón	REM	PRISMA	High	RCT Case-control Retrospectives	Standard treatment /PBO	Mortality Hospital discharge Reduct. days hospitalization	17 13 4	1293 864 240	0.61 (0.49-0.76; NA) 1.04 (0.86-1.24; NA) -1.96 (-4.24-0.33; NA)	MED: 58% HIGH: 82% MED: 41%	S: 0.273 S: 0.022 -
2021	Rezaei	REM	PRISMA, Cochrane	High	RCT Cohorts Case-control	Standard treatment	Mortality (ECA) Mortality (COH) Mortality (CC) Clinical improvement (RCT) Idem (Cohort Idem (Case-control)	4 26 16 1 4 1	578 2661 760 - - -	1.04 (0.73-1.48; 0,937) 0.82 (0.66-1.01; 0,000) 0.62 (0.47-0.82; NA) 1.19 (0.95-1.49; NA) 1.11 (0.87-1.43; 0,135) 1.45 (1.14-1.85; NA)	LOW: 0% HIGH: 81.3% MED: 66.5% LOW: 0% MED: 46.1% LOW: 0%	No association No association S: 0.264 No association No association No association

Tabla S2. Interleukin 6 (IL-6) inhibitors: Tocilizumab. Meta-analysis of its effectiveness in the treatment of COVID-19. Continuation.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2021	Rubio-Rivas	REM	PRISMA	High	Observational RCT	Standard treatment	Mortality	64	7668	0.73 (0.56-0.93;<0.001)	HIGH: 82%	S: 0,174
2021	Snow	REM	PRISMA, Cochrane	High	RCT	Standard treatment /PBO	Mortality days 28-30	9	3358	0.87 (0.74-1.01; 0.07)	LOW: 10%	No association
2021	Tharmarajah	REM/ NMA	PRISMA, Cochrane	High	RCT: Tocilizumab + Sarilumab	Standard treatment /PBO	Mortality day 28	9	3647	0.90 (0.81-0.99; NA)	LOW: 0%	S: 0,058
2021	Tleyjeh	REM	Cochrane	High	RCT Observational	Standard treatment /PBO	Mortality Infection risk Infection risk	8 8 28	6311 5340 15484	0.91 (0.78-1.07; NA) 0.67 (0.45-0.99; NA) 0.53 (0.43-0.67; NA)	LOW: 25% MED: 45% HIGH: 76%	No association S: 0,221 S: 0,350
2021	Viswanatha	REM	PRISMA, Cochrane	High	Observational retrospective	Standard treatment /PBO	Mortality ICU admission MV	22 8 12	1841 635 756	-0.11 (-0.18; -0.04; NA) -2.86 (-9.10; 3.38; NA) 0.00 (-0.06; 0.07; NA)	HIGH: 88% HIGH: 100% MED: 74%	No association No association No association
2021	Wei	REM	PRISMA, Cochrane	High	Observational RCT	Standard treatment	Mortality	13	NA	0.45 (0.24-0.81;0.01)	HIGH: 99%	S: 0,440
2021	WHO	REM/ FEM	WHO	High	RCT	Standard treatment /PBO	Mortality day 28	19	4299	0.83 (0.74-0.92;<0.001)	ND	S: 0,103
2022	Luo	REM	PRISMA, Cochrane	High	RCT	Standard treatment	Mortality days 28-30 Total Mortality MV Secondary infection	9 9 6 8	3039 3991 2462 1336	0.91 (0.83-0.99; NA) 0.91 (0.84-0.98; NA) 0.81 (0.70-0.95; NA) 0.74 (0.50-1.08; NA)	LOW: 3% LOW: 0% LOW: 0% MED: 42%	S: 0,052 S: 0,052 S: 0,116 No association
2022	Peng (a)	REM	PRISMA	High	RCT Case-control	Standard treatment	Mortality Secondary infection risk	5 24	827 2224	0.74 (0.58-0.94;0.013) 1.12 (0.87-1.43;0.376)	MED: 61,5% MED: 55,8%	S: 0,166 No association
2022	Peng (b)	REM/ FEM	PRISMA, Cochrane	High	RCT	Standard treatment	Mortality Hospital discharge	10 8	3378 3038	0.89 (0.82-0.96;0.003) 1.13 (1.08-1.18;<0.00001)	LOW: 28% LOW: 34%	S: 0,064 S: 0,067
2022	Vela	FEM	PRISMA, Cochrane	High	RCT	Standard treatment /PBO	Mortality all causes MV	10 9	3528 3042	0.88 (0.81-0.95; 0.0009) 0.79 (0.71-0.88; 0.0001)	LOW: 10% LOW: 0%	S: 0,070 S: 0,130
2022	Yu	REM	PRISMA	High	RCT	Standard treatment /PBO	Mortality day 28 Progression to MV	12 8	7369 5392	0.89 (0.82-0.95; NA) 0.79 (0.71-0.88; NA)	LOW: 0% LOW: 0%	S: 0,064 S: 0,130
2023	Albuquerque	Bayesian model	PRISMA	High	RCT (+ corticoids)	Standard treatment /PBO	Mortality day 28	16	3042	0.78 (0.65-0.94; NA)	NA	S: 0,137

*The following criteria were used: (i) up to 25%, low heterogeneity (LOW); (ii) between > 25% and < 75%, moderate heterogeneity (MED); and, finally, (iii) if ≥ 75%, high heterogeneity (HIGH) (*Higgins, 2003*); ** By convention, for Cohen's "d" of 0-0.4; 0.5-0.7 and ≥ 0.8 are considered small (S), medium (M) and large (L) effect sizes respectively (*Chen, 2010*). Cohen's d was calculated using the tool available at the following URL: https://www.escal.site/. § References: PRISMA: *Liberati, 2009; Moher, 2009; Page, 2021; Cochrane: Cochrane, 2022; WHO: Shankar-Hari, 2021*. # Reference: *National, 2023*; ¶ Non randomized prospective cohort studies. Abbreviations: 95% CI: 95% confidence interval; FEM: fixed effects model; HIGH: high heterogeneity; HR: hazard ratio; L: large effect; LOW: low heterogeneity; M: medium effect; MED: average heterogeneity; MV: mechanical ventilation; NHLBI: National Heart, Lung and Blood Institute (*National, 2023*); NA: not available; NMA: network meta-analysis; OR: odds ratio; p: statistical significance; PBO: placebo; RCT: randomized clinical trials; REM: random effects model; RR: relative risk; S: small effect.

Tabla S3. Interleukin 6 (IL-6) inhibitors: Sarilumab. Meta-analysis of its effectiveness in the treatment of COVID-19.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2021	Ghosn	REM	Cochrane	High	RCT	Standard treatment/PBO	Mortality day 28	2	880	0.77 (0.43-1.36; NA)	MOD: 32.3%	No association
2021	Peng	REM	PRISMA	High	RCT Case-control	Standard treatment	Mortality Secondary infection	1	28	0.40 (0.07-2.24; 0.297) 1.20 (0.33-4.39; 0.783)	NA NA	No association No association
2021	Tharmarajah	REM NMA	PRISMA. Cochrane	High	RCT: Tocilizumab + Sarilumab	Standard treatment/PBO	Mortality day 28	9	3647	0.90 (0.81-0.99; NA)	LOW: 0%	S: 0.058
2021	WHO	FEM/ REM	WHO	High	RCT	Standard treatment/PBO	Mortality day 28	9	2073	1.08 (0.86-1.36;0.52)	LOW: 0%	No association
2022	Yu	REM	PRISMA	High	RCT	Standard treatment/PBO	Mortality day 28 VM progression	6 1	1483 115	0.81 (0.59-1.10; NA) 1.15 (0.38-3.51; NA)	NA NA	No association No association
2023	Albuquerque	Bayesian	PRISMA	High	RCT (+ corticoids)	Standard treatment/PBO	Mortality day 28	8	703	0.91 (0.60-1.40; NA)	NA	No association

*The following criteria were used: (i) up to 25%, low heterogeneity (LOW); (ii) between > 25% and < 75%, moderate heterogeneity (MED); and, finally, (iii) if ≥ 75%, high heterogeneity (HIGH) (*Higgins, 2003*); ** By convention, for Cohen's "d" of 0-0.4; 0.5-0.7 and ≥ 0.8 are considered small (S), medium (M) and large (L) effect sizes respectively (*Chen, 2010*). Cohen's d was calculated using the tool available at the following URL: https://www.escal.site/. § References: PRISMA: *Liberati, 2009; Moher, 2009; Page, 2021; Cochrane: Cochrane, 2022; WHO: Shankar-Hari, 2021*. # Reference: *National, 2023*; ¶ Non randomized prospective cohort studies. Abbreviations: 95% CI: 95% confidence interval; FEM: fixed effects model; HIGH: high heterogeneity; HR: hazard ratio; L: large effect; LOW: low heterogeneity; M: medium effect; MED: average heterogeneity; MV: mechanical ventilation; NHLBI: National Heart, Lung and Blood Institute (*National, 2023*); NA: not available; NMA: network meta-analysis; OR: odds ratio; p: statistical significance; PBO: placebo; RCT: randomized clinical trials; REM: random effects model; RR: relative risk; S: small effect.

Table S4 (a). Monoclonal antibodies. Meta-analysis of its effectiveness in the treatment of COVID-19.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Monoclonal antibody Comparator	COVID-19 variants results	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2021	Siemieniuk	NMA	PRISMA, Cochrane	High	RCT	**Casirivimab-Imdevimab** Standard treatment	NA	*Non-serious illness*: Hospitalization risk Mortality MV *Serious illness:* Mortality **Sotrovimab** *Non-serious illness*: Hospitalization risk Mortality MV	 4 4 4 4 1 1 1	 NA NA NA NA NA NA NA	 0.29 (0.17-0.47; NA) 0.58 (0.26-1.22; NA) 0.21 (0.02-1.20; NA) 0.94 (0.58-1.52; NA) 0.17 (0.04-0.57; NA) 0.33 (0.01-10.16; NA) 0.20 (0.01-5.07; NA)	 NA NA NA NA NA NA NA	 M: 0.682 No association No association No association L: 0.977 No association No association
2022	Amani	REM FEM	PRISMA	High	RCT Observational	**Sotrovimab** Standard treatment	Delta, Omicron	Mortality Hospitalization risk MV	15 13 6	NA NA NA	0.40 (0.25-0.63; 0.000) 0.53 (0.43-0.65; 0.000) 0.57 (0.33-0.96; 0.037)	NA NA NA	M: 0.505 S: 0.350 S: 0.310
2022	McConnell	NMA	PRISMA, Cochrane	High	RCT	**Casirivimab-Imdevimab** Placebo vs antibody **Sotrovimab** Placebo vs antibody	NA	Mortality Hospitalization risk MV Mortality Hospitalization risk MV	1 1 1 2 2 2	NA NA NA NA NA NA	7.69 (1.77-40.63;<0.05) 3.70 (2.21-6.22;<0.05); 4.96 (1.10-32.38;<0.05) 13.70 (0.75-842.5;<0.05) 4.95 (180-14.86;<0.05) 20.61 (1.36-1147;<0.05)	NA NA NA NA NA NA	L: 1.125 M: 0.721 L: 0.083 L: 1.443 L: 0.082 L: 1.668
2022	Yang***	NA	Cochrane	High	RCT Observational	**Regdanvimab**	NA	Mortality	4	789	0.14 (0.03-0.56;0.006)	LOW: 0%	L: 1.084
2023	Deng	NMA	PRISMA, Cochrane	High	RCT	**Casirivimab-Imdevimab** Standard treatm/PBO **Sotrovimab** Standard treatm/PBO	NA	Mortality Hospitalization risk Mortality	NA NA NA	NA NA NA	0.67 (0.50-0.91; NA) 0.29 (0.20-0.42; NA) 0.20 (0.08-0.48; NA)	NA NA NA	S: 0.221 M: 0.682 L: 0.887

*The following criteria were used: (i) up to 25%, low heterogeneity (LOW); (ii) between > 25% and < 75%, moderate heterogeneity (MED); and, finally, (iii) if ≥ 75%, high heterogeneity (HIGH) (*Higgins, 2003*); ** By convention, for Cohen's "d" of 0-0.4; 0.5-0.7 and ≥ 0.8 are considered small (S), medium (M) and large (L) effect sizes respectively (*Chen, 2010*). Cohen's d was calculated using the tool available at the following URL: https://www.escal.site/. § References: PRISMA: *Liberati, 2009; Moher, 2009; Page, 2021; Cochrane: Cochrane, 2022; WHO: Shankar-Hari, 2021*. # Reference: *National, 2023*; ¶ Non randomized prospective cohort studies. Abbreviations: 95% CI: 95% confidence interval; FEM: fixed effects model; HIGH: high heterogeneity; HR: hazard ratio; L: large effect; LOW: low heterogeneity; M: medium effect; MED: average heterogeneity; MV: mechanical ventilation; NHLBI: National Heart, Lung and Blood Institute (*National, 2023*); NA: not available; NMA: network meta-analysis; OR: odds ratio; p: statistical significance; PBO: placebo; RCT: randomized clinical trials; REM: random effects model; RR: relative risk; S: small effect.

Table S4 (b). Clinical studies on mortality published in the years 2022 and 2023 (until October) of the treatment of COVID-19 with cilgavimab/tixagevimab (PubMed).

Year	Author	Study type	Patients	Results by COVID-19 variants	Arms	N	Mortality	HR, RR (IC 95%)	P
2022	ACTIV-3	RCT	COVID-19 Hospitalized	NA	Treated Placebo	710 707	9% 12%	0.70 (0.50;0.97)	0.032
2023	Kertes	Cohorts	COVID-19 Immunocompromised	NA	Treated Untreated	825 4299	0% 0,9%	-	0.005
2023	Wang	Meta-analysis	COVID-19	NA	Treated Placebo	5383 7152	-	0.50 (0.39;0.64)	<0.01

RCT: randomized clinical trials; HR: hazard ratio; N: sample size; NA: not available; RR: relative risk.

Table S5. Hydroxychloroquine and chloroquine. Meta-analysis of its effectiveness in the treatment of COVID-19.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2020	Elavarasi	REM	PRISMA, Cochrane	High	Observational RCT	Standard treatment	Mortality MV	7 6	4295 2071	0.98 (0.66-1.46; NA) 0.90 (0.47-1.71; NA)	HIGH: 87% HIGH: 87%	No association No association
2020	Ghazy	REM	PRISMA, Cochrane	High	Observational RCT	Standard treatment/PBO	Mortality	8	1671	0.99 (0.61-1.59; 0.96)	HIGH: 82%	No association
2020	Kashour	REM	PRISMA, Cochrane	High	RCT Cohorts	Standard treatment/PBO	Mortality	13	-	0.93 (0.79-1.11; NA)	MED:59%	No association
2020	Pathak	REM	Cochrane	High	RCT	Standard treatment	Ni Mortality ni VM	7	1721	1.11 (0.72-1.69; NA)	MED: 32%	No association
2020	Sarma	REM	PRISMA, Cochrane	High	Observational RCT	Standard treatment	Virological cure Mortality/deterioration	2 3	29 66	2.37 (0.13-44.53; NA) 1.37 (0.09-21.97; NA)	MED: 72% MED: 59%	No association No association
2020	Singh	REM	PRISMA, Cochrane	High	Observational RCT	Standard treatment/PBO	Negative PCR Mortality	3 3	210 474	1.05 (0.79-1.38; 0.74) 2.17 (1.32-3.56; 0.002)	MED: 61.7% LOW: 0%	No association S: 0.427
2021	Amani	REM	PRISMA, Cochrane	High	RCT	Standard treatment/PBO	Negative PCR Mortality MV Disease progression	4 4 4 4	460 2764 2503 465	0.99 (0.90-1.08; NA) 1.09 (1.00-1.20; NA) 1.12 (0.95-1.32; NA) 0.82 (0.37-1.85; NA)	LOW: 0% LOW: 0% LOW: 0% LOW: 11%	No association No association No association No association
2021	Axfors	REM	PRISMA, Cochrane WHO	High	RCT	Standard treatment/PBO	Dead Hydroxychloroquine Dead Chloroquine	14 5	3809 160	1.12 (1.08-1.16; NA) 1.77 (0.15-21.13; NA)	LOW: 0% LOW: 0%	No association No association
2021	Celotto	REM	PRISMA	High	Metaanálisis	PBO	Mortality	6	NA	Higher risk of death	NA	-
2021	Chi	NMA	Cochrane	High	RCT	Standard treatment/PBO	Mortality MV	NA NA	NA NA	1.12 (0.99-1.26; NA) 1.12 (0.94-1.34; NA)	NA NA	No association No association
2021	Chivese	REM	PRISMA, Cochrane	High	Metaanálisis	Standard treatment/PBO	Mortality	NA	NA	1.1 (1.0-1.3; NA)	LOW: 0%	No association
2021	Elsawah	REM/ FEM	PRISMA, Cochrane	High	RCT Observational	Standard treatment	Mortality 5 días	4	249	0.01 (-0.01;0.03; NA)	LOW: 0%	No association
2021	Fiolet	REM	PRISMA, Cochrane	High	RCT Observational	Standard treatment	Mortality	17	NA	0.83 (0.65-1.06; NA)	HIGH: 83%	No association
2021	García-Albéniz	REM/ FEM	PRISMA, Cochrane	High	RCT	Standard treatment/PBO	Pre-exposure prophylaxis Post-exposure prophylaxis	7 4	NA NA	0.72 (0.58-0.90; NA) 0.91 (0.72-1.16; NA)	LOW: 0% LOW: 0%	S: 0.181 No association

Table S5. Hydroxychloroquine and chloroquine. Meta-analysis of its effectiveness in the treatment of COVID-19. Continuation.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2021	Singh (a)	REM	Cochrane	High	RCT	Standard treatment/PBO	Mortality MV	9 3	8208 4521	1.09 (0.99-1.19; ND) 1.11 (0.91-1.37; ND)	LOW: 0% LOW: 0%	No association No association
2022	Gupta	REM	PRISMA, Cochrane	High	RCT	Standard treatment/PBO	Clinical improvement day 28 Mortality day 28	9 14	1606 3788	1.00 (0.96-1.03; ND) 1.08 (0.99-1.19; ND)	MED: 51% LOW: 0%	No association No association

*The following criteria were used: (i) up to 25%, low heterogeneity (LOW); (ii) between > 25% and < 75%, moderate heterogeneity (MED); and, finally, (iii) if ≥ 75%, high heterogeneity (HIGH) (*Higgins, 2003*); ** By convention, for Cohen's "d" of 0-0.4; 0.5-0.7 and ≥ 0.8 are considered small (S), medium (M) and large (L) effect sizes respectively (*Chen, 2010*). Cohen's d was calculated using the tool available at the following URL: https://www.escal.site/. § References: PRISMA: *Liberati, 2009; Moher, 2009; Page, 2021; Cochrane: Cochrane, 2022; WHO: Shankar-Hari, 2021*. # Reference: *National, 2023*; ¶ Non randomized prospective cohort studies. Abbreviations: 95% CI: 95% confidence interval; FEM: fixed effects model; HIGH: high heterogeneity; HR: hazard ratio; L: large effect; LOW: low heterogeneity; M: medium effect; MED: average heterogeneity; MV: mechanical ventilation; NHLBI: National Heart, Lung and Blood Institute (*National, 2023*); NA: not available; NMA: network meta-analysis; OR: odds ratio; p: statistical significance; PBO: placebo; RCT: randomized clinical trials; REM: random effects model; RR: relative risk; S: small effect.

Table S6 (a). Antivirals: Remdesivir. Meta-analysis of its effectiveness in the treatment of COVID-19.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2021	Jiang	NMA	Cochrane	High	RCT	10 days vs PBO 5 days vs PBO	Clinical improvement day 10-15*** Clinical recovery follow-up	3 1	779 191	1.35 (1.09-1.67; NA) 1.81 (1.32-2.45; NA)	NA NA	S: 0.165 S: 0.327
2021	Lai	NMA	PRISMA, Cochrane	High	RCT	5 days vs PBO/TE 10 days vs PBO/TE	Clinical improvement Mortality Clinical improvement Mortality	3 4 3 4	ND ND ND ND	1.68 (1.18-2.40; NA) 0.50 (0.24-1.04; NA) 1.23 (0.90-1.68; NA) 0.74 (0.54-1.03; NA)	LOW: 0% LOW: 0% LOW: 0% LOW: 0%	S: 0.286 No association No association No association
2021	Shrestha	REM FEM	PRISMA	High	RCT	Standard treatment/PBO	Clinical improvement day 14 Clinical improvement day 28 Mortality day 14 Mortality day 28 Clinical recovery day 14 Clinical recovery day 28	2 2 3 2 2 1	351 351 889 351 487 178	1.45 (1.00-2.08; 0.05) 1.59 (1.06-2.39; 0.02) 0.61 (0.41-0.91; 0.01) 1.02 (0.50-2.06; 0.96) 1.48 (1.19-1.84; 0.00) 2.09 (1.09-4.03; 0.03)	LOW: 0% LOW: 0% LOW: 0% LOW: 0% LOW: 0% -	No association S: 0.256 S: 0.273 No association S: 0.216 L: 0.406
2021	Singh (b)	REM FEM	PRISMA, Cochrane	High	RCT	Standard treatment	Clinical improvement Mortality Time to clinical improvement	3 1 2	1080 3818 ND	1.52 (1.24-1.87;<0.0001) 0.92 (0.79-1.07;0.3) 1.28 (1.12-1.46;0.0002)	LOW: 0% LOW: 0% LOW: 0%	S: 0.231 No association S: 0.136
2022	Angamo	FEM	PRISMA, Cochrane	High	RCT Observational	Standard treatment/PBO	Clinical recovery day 7 Clinical recovery day 14 Clinical recovery day 28	4 5 4	1080 1392 1083	1.21 (1.08-1.35;0.0008) 1.29 (1.22-1.37;0.00001) 1.09 (1.04-1.14;0.0002)	MED: 29% HIGH: 76% LOW: 0%	S: 0.105 S: O.140 S: 0.048
2022	Beckerman	NMA	PRISMA	High	RCT	Standard treatment/PBO	Early mortality Late mortality Early clinical recovery Late clinical recovery	6 6 6 6	924 2791 2752 2783	0.52 (0.34-0.79; NA) 0.81 (0.69-0.95; NA) 1.01 (0.97-1.06; NA) 1.03 (1.00-1.06; NA)	NA NA NA NA	S: 0.361 S: 0.116 No association No association
2022	Kaka	FEM	Cochrane	High	RCT	10 días vs PBO/TE 10 días vs PBO/TE	Mortality MV	4 3	3635 887	0.93 (0.82-1.06; NA) 0.71 (0.56-0.90; NA)	LOW: 6% MED: 38%	No association S: 0.189
2022	Lee	REM	PRISMA, Cochrane	High	RCT	Standard treatment/PBO	Mortality with MV Mortality w/o MV Mortality w/o oxygen	4 7 5	504 3689 1339	1.08 (0.88-1.31;0.353) 0.89 (0.79-0.99;0.363) 0.77 (0.50-1.19;0.420)	LOW: 8% LOW: 8.6% LOW: 2.9%	No association No association No association
2022	WHO****	RCT	ND	ND	RCT	Standard treatment	Mortality	ND	4146	0.91 (0.82-1.02;0.12)	NA	No association

Table S6 (a). Antivirals: Remdesivir. Meta-analysis of its effectiveness in the treatment of COVID-19. Continuation.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2023	Grundeis	REM	Cochrane	High	RCT	Standard treatment/ PBO	Mortality day 28	4	7142	0.93 (0.81-1.06; 0.28)	LOW: 0%	No association
							Mortality day 60	1	1281	0.85 (0.69-1.05; 0.13)	-	No association
							In-hospital mortality day 150Clinical	1	8275	0.93 (0.84-1.03; 0.18)	-	No association
							improvement day 28	4	2514	1.11 (1.06-1.17;0.0001)	LOW: 0%	No association
							Clinical worsening day 28	2	1734	0.67 (0.54-0.82;<0.0001)	LOW: 0%	S: 0.221

*The following criteria were used: (i) up to 25%, low heterogeneity (LOW); (ii) between > 25% and < 75%, moderate heterogeneity (MED); and, finally, (iii) if ≥ 75%, high heterogeneity (HIGH) (*Higgins, 2003*); ** By convention, for Cohen's "d" of 0-0.4; 0.5-0.7 and ≥ 0.8 are considered small (S), medium (M) and large (L) effect sizes respectively (*Chen, 2010*). Cohen's d was calculated using the tool available at the following URL: https://www.escal.site/. § References: PRISMA: *Liberati, 2009; Moher, 2009; Page, 2021; Cochrane: Cochrane, 2022; WHO: Shankar-Hari, 2021*. # Reference: *National, 2023*; ¶ Non randomized prospective cohort studies. Abbreviations: 95% CI: 95% confidence interval; FEM: fixed effects model; HIGH: high heterogeneity; HR: hazard ratio; L: large effect; LOW: low heterogeneity; M: medium effect; MED: average heterogeneity; MV: mechanical ventilation; NHLBI: National Heart, Lung and Blood Institute (*National, 2023*); NA: not available; NMA: network meta-analysis; OR: odds ratio; p: statistical significance; PBO: placebo; RCT: randomized clinical trials; REM: random effects model; RR: relative risk; S: small effect.

Table S6 (b). Mortality clinical studies published in 2023 (through October) of COVID-19 treatment with remdesivir (PubMed).

Year	Author	Study type	Patients	Treatments	N	Mortality	OR, HR, RR (95% CI)	P
2023	Amstutz	RCT meta-analysis	COVID-19 Hospitalized	Remdesivir Placebo/Standard	5398 5082	All causes day 28 All causes day 60	OR=0.88 (0.78;1.00) OR=0.91 (0.81;1.02)	0.045 0.116
2023	Huang	RCT meta-analysis	COVID-19 (w/o O_2 supplement)	Remdesivir Placebo/ Standard	2230 2151	All causes day 28	RR= 0.83 (0.71;0.98)	0.02
2023	Marx	Retrospective cohorts	COVID-19 Hospitalized	Remdesivir + corticoids Only corticoids	260 260	All causes day 28	HR= 0.60 (0.39;0.95)	0.03
2023	Metchurt-chlishvili	Prospective cohorts	COVID-19 Hospitalized	Remdesivir Placebo/Standard	346 346	All causes	2.3% 5.2%	0.046
2023	Mozaffari (a)	Retrospective cohorts	COVID-19 Hospitalized	Remdesivir (LOF) Remdesivir (NIV) Remdesivir (IV) No remdesivir (LOF) No remdesivir (NIV) No remdesivir (IV)	67582 34857 4164 10830 10189 1880	All causes day 14 All causes day 14 All causes day 14 All causes day 28 All causes day 28 All causes day 28	HR= 0.72 (0.66;0.79) HR= 0.83 (0.77;0.89) HR= 0.73 (0.65;0.82) HR= 0.79 (0.73;0.85) HR= 0.88 (0.82;0.93) HR= 0.74 (0.67;0.82)	-
2023	Mozaffari (b)	Retrospective cohorts	COVID-19 Immunocompromised	Remdesivir No remdesivir	19184 11213	All causes day 14 All causes day 28	HR= 0.70 (0.62;0.78) HR= 0.75 (0.68;0.83)	-

RCT: randomized clinical trials; HR: hazard ratio; IV: invasive ventilation; LOF: low oxygen flow; N: sample size; NIV: non-invasive ventilation; RR: relative risk.

Table S7. Antivirals: Favipiravir. Meta-analysis of its effectiveness in the treatment of COVID-19.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2020	Shrestha	REM FEM	PRISMA, Cochrane	High	RCT Observational	Other antivirals Standard treatment	Viral elimination day 7 Viral elimination day 14 Clinical improvement day 7 Clinical improvement day 14	3 3 3 3	84 84 160 84	1.13 (0.55-2.33; 0.73) 1.06 (0.84-1.33; 0.65) 1.25 (1.01-1.53; 0.04) 1.29 (1.08-1.54; 0.005)	HIGH: 84% MED: 67% LOW: 0% LOW: 16%	No association No association S: 0.123 S: 0.140
2021	Hassanipour	REM	PRISMA	High	RCT	Standard treatment	Viral elimination Clinical improvement	6 8	ND ND	1.06 (0.98-1.14; ND) 1.17 (1.07-1.28; ND)	ND ND	No association No association
2021	Özlüşen	REM	PRISMA, Cochrane	High	RCT Observational	Standard treatment	Mortality MV	12 8	823 619	1.11 (0.64-1.94;0.69) 0.50 (0.13-1.95;<0.01)	LOW: 0% HIGH: 75%	No association S: 0.382
2022	Hung	FEM	PRISMA, Cochrane	High	RCT Observational	Standard treatment	Viral elimination day 5 Viral elimination day 10 Clinical improvement day 10	7 7 8	246 310 881	1.75 (1.11-2.77;0.02) 1.19 (1.06-1.34;<0.01) 1.27 (0.88-1.85;0.17)	MED: 54% MED: 41% HIGH: 73%	S: 0.309 S: 0.096 No association

*The following criteria were used: (i) up to 25%, low heterogeneity (LOW); (ii) between > 25% and < 75%, moderate heterogeneity (MED); and, finally, (iii) if ≥ 75%, high heterogeneity (HIGH) (*Higgins, 2003*); ** By convention, for Cohen's "d" of 0-0.4; 0.5-0.7 and ≥ 0.8 are considered small (S), medium (M) and large (L) effect sizes respectively (*Chen, 2010*). Cohen's d was calculated using the tool available at the following URL: https://www.escal.site/. § References: PRISMA: *Liberati, 2009; Moher, 2009; Page, 2021; Cochrane: Cochrane, 2022; WHO: Shankar-Hari, 2021*. # Reference: *National, 2023*; ¶ Non randomized prospective cohort studies. Abbreviations: 95% CI: 95% confidence interval; FEM: fixed effects model; HIGH: high heterogeneity; HR: hazard ratio; L: large effect; LOW: low heterogeneity; M: medium effect; MED: average heterogeneity; MV: mechanical ventilation; NHLBI: National Heart, Lung and Blood Institute (*National, 2023*); NA: not available; NMA: network meta-analysis; OR: odds ratio; p: statistical significance; PBO: placebo; RCT: randomized clinical trials; REM: random effects model; RR: relative risk; S: small effect.

Table S8. Antivirals: Nirmatrelvir-Ritonavir. Meta-analysis of its effectiveness in the treatment of COVID-19.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2022	Reis	REM	Cochrane	High	RCT	Standard treatment/PBO	Mortality day 28 Deterioration day 28	1 1	2224 1109	0.04 (0.00-0.68;0.03) 0.13 (0.07-0.27;<0.00001)	- -	L: 1.775 L: 1.125
2023	Amani	REM FEM	PRISMA, Cochrane	High	RCT Observational	Standard treatment/PBO	Mortality Hospitalization	13 11	NA NA	0.25 (0.14-0.45; 0.000) 0.41 (0.24-0.69; 0.001)	NA NA	M: 0.787 M: 0.492
2023	Cheema	REM	Cochrane	High	RCT Observational	No treatment/ PBO	Mortality Hospitalization	10 11	NA NA	0.24 (0.15-0.39;<0.00001) 0.41 (0.29-0.59;<0.00001)	MED: 48% HIGH: 90%	M: 0.787 M: 0.492

*The following criteria were used: (i) up to 25%, low heterogeneity (LOW); (ii) between > 25% and < 75%, moderate heterogeneity (MED); and, finally, (iii) if ≥ 75%, high heterogeneity (HIGH) (*Higgins, 2003*); ** By convention, for Cohen's "d" of 0-0.4; 0.5-0.7 and ≥ 0.8 are considered small (S), medium (M) and large (L) effect sizes respectively (*Chen, 2010*). Cohen's d was calculated using the tool available at the following URL: https://www.escal.site/. § References: PRISMA: *Liberati, 2009; Moher, 2009; Page, 2021; Cochrane: Cochrane, 2022; WHO: Shankar-Hari, 2021*. # Reference: *National, 2023*; ¶ Non randomized prospective cohort studies. Abbreviations: 95% CI: 95% confidence interval; FEM: fixed effects model; HIGH: high heterogeneity; HR: hazard ratio; L: large effect; LOW: low heterogeneity; M: medium effect; MED: average heterogeneity; MV: mechanical ventilation; NHLBI: National Heart, Lung and Blood Institute (*National, 2023*); NA: not available; NMA: network meta-analysis; OR: odds ratio; p: statistical significance; PBO: placebo; RCT: randomized clinical trials; REM: random effects model; RR: relative risk; S: small effect.

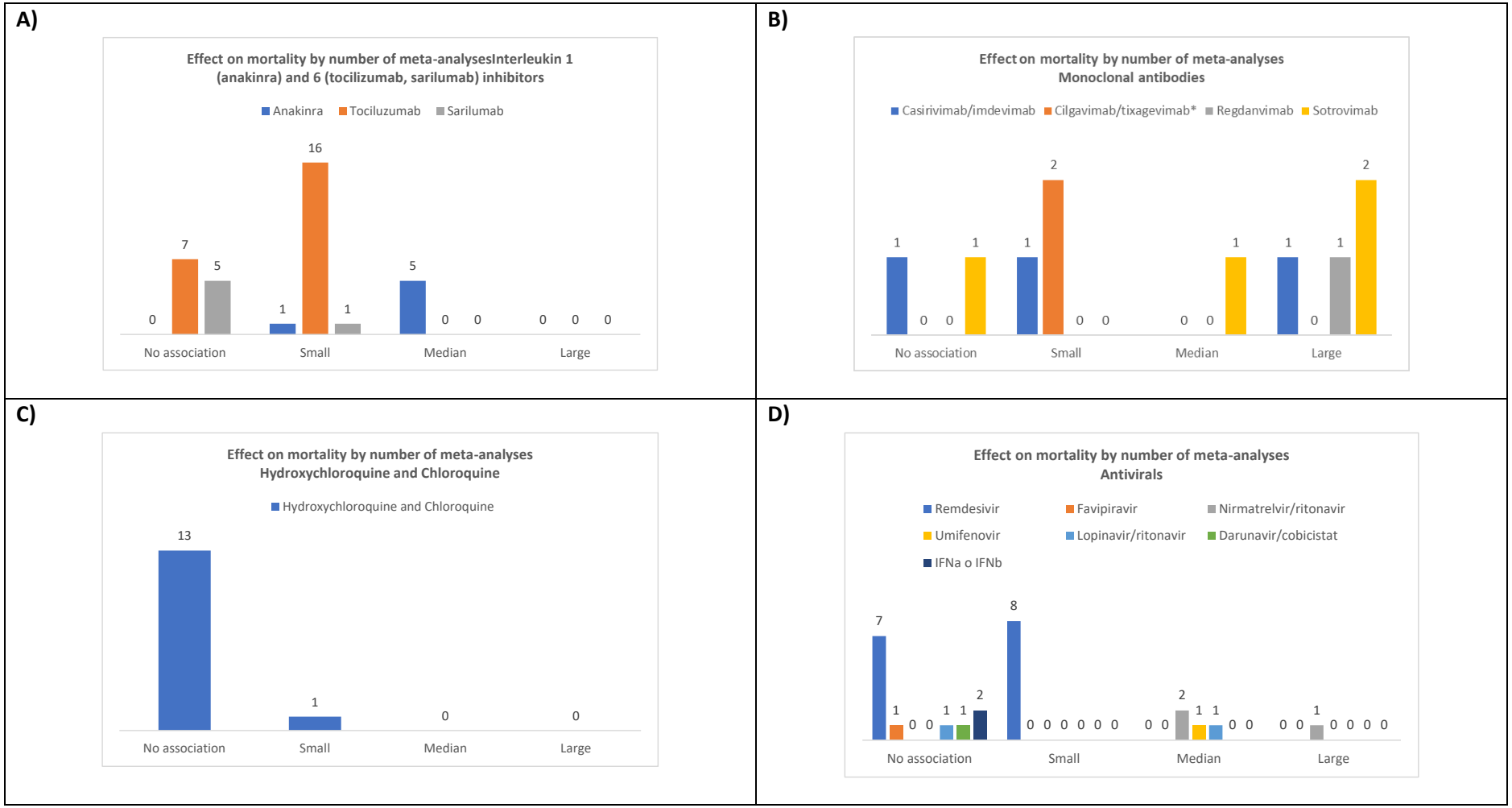
Table S9. Other antivirals. Meta-analysis of its effectiveness in the treatment of COVID-19.

Year	First author	Meta-analysis type	PRISMA / Cochrane / WHO §	Quality NHLBI #	Clinical trials design	Comparator	Main efficacy endpoints	No studies included	No patients included	OR/RR/HR (95% CI; p)	Hetero-geneity (I^2) *	Magnitude of effect: Cohen's "d" **
2020	Huang	REM	PRISMA, Cochrane	High	RCT Observational	**Umifenovir** Standard treatment	Negative PCR	5	140	1.27 (1.04-1.55;0.02)	MED: 63%	S: 0.132
2021	Wu	REM	Cochrane	High	RCT Observational	**Lopinavir/ritonavir** Standard treatment	Mortality Viral elimination	12 5	542 288	0.43 (0.25-0.73;0.002) 2.39 (1.68-3.39;<0.00001)	LOW: 0% HIGH: 83%	M: 0.465 M: 0.480
2021	Yu	FEM	PRISMA, Cochrane	High	RCT	**Umifenovir** **Lopinavir/ritonavir**	Mortality	3	84	0.32 (0.10-1.09;0.07)	LOW: 0%	No association
2022	Chen	REM FEM	PRISMA, Cochrane	High	RCT	**INF-b** Standard treatment	Mortality	8	2488	0.74 (0.44-1.24;0.25)	MED: 51%	No association
2022	Okoli ***	NMA	PRISMA, Cochrane	High	RCT	**Darunavir/cobicistat** Standard treatment	Mortality Clinical improvement Viral elimination	NA	NA	1.00 (0.02-5.10; NA) 0.94 (0.66-1.26; NA) 1.40 (0.25-4.57; NA)	NA	No association No association No association
						IFN-alpha Standard treatment	Mortality Clinical improvement Viral elimination	NA	NA	1.12 (0.94-1.33; NA) NA NA	NA	No association - -
						INF-beta Standard treatment	Mortality Clinical improvement Viral elimination	NA	NA	0.43 (0.08-1.18; NA) 1.16 (0.80-1.63; NA) NA	NA	No association No association -
						Lopinavir/ritonavir Standard treatment	Mortality Clinical improvement Viral elimination	NA	NA	0.95 (0.78-1.15; NA) 1.07 (0.81-1.40; NA) 1.06 (0.74-1.50; NA)	NA	No association No association No association
						Ribavirin Standard treatment	Mortality Clinical improvement Viral elimination	NA	NA	0.73 (0.06-2.71; NA) NA 0.72 (0.40-1.14; NA)	NA	No association - No association
2023	Buchynskyi	REM FEM	PRISMA, Cochrane	High	RCT Observational	**IFN-alpha** Standard treatment	Mortality	9	NA	0.25 (0.05-1.19; 0.082)	NA	No association

*The following criteria were used: (i) up to 25%, low heterogeneity (LOW); (ii) between > 25% and < 75%, moderate heterogeneity (MED); and, finally, (iii) if ≥ 75%, high heterogeneity (HIGH) (*Higgins, 2003*); ** By convention, for Cohen's "d" of 0-0.4; 0.5-0.7 and ≥ 0.8 are considered small (S), medium (M) and large (L) effect sizes respectively (*Chen, 2010*). Cohen's d was calculated using the tool available at the following URL: https://www.escal.site/. § References: PRISMA: *Liberati, 2009; Moher, 2009; Page, 2021; Cochrane: Cochrane, 2022; WHO: Shankar-Hari, 2021*. # Reference: *National, 2023*; ¶ Non randomized prospective cohort studies. Abbreviations: 95% CI: 95% confidence interval; FEM: fixed effects model; HIGH: high heterogeneity; HR: hazard ratio; L: large effect; LOW: low heterogeneity; M: medium effect; MED: average heterogeneity; MV: mechanical ventilation; NHLBI: National Heart, Lung and Blood Institute (*National, 2023*); NA: not available; NMA: network meta-analysis; OR: odds ratio; p: statistical significance; PBO: placebo; RCT: randomized clinical trials; REM: random effects model; RR: relative risk; S: small effect.

SUPLEMENT 6. SUPPLEMENTARY FIGURES

Figure S1. Effects on mortality from COVID-19 by number of published meta-analyses.



SUPLEMENT 7.

SUPPLEMENT 7. STUDIES EXCLUDED IN THE BASE CASE FOR BEING PUBLISHED IN JOURNALS WITH LOW IMPACT FACTOR (< 1)

Drug	Year	First author	Guidelines	Main efficacy endpoint	Studies design	N patients exp. Drug	OR/RR/HR (95% CI; p)	Magnitude of effect: Cohen's d*
Immunomodulators								
Immunomodulators	2020	Talaie	PRISMA	Mortality	OBS, RCT	271	0.22 (0.09;0.53)	L: 0.835
Anakinra	2022	Malik	PRISMA	Mortality	OBS, RCT	565	0.47 (0.37;0.59)	S: 0.416
Anakinra	2022	Naveed	PRISMA	Mortality	OBS, RCT	917	0.64 (0.49;0.83;<0.001)	S: 0.246
Anakinra	2023	Dahms	-	Mortality	RCT	888	0.96 (0.64;1.45)	No association
Anti-IL6 (tocilizumab, sarilumab)	2022	Alegre	PRISMA	Mortality	RCT	6,349§	0.85 (0.74;0.99)	S: 0.090
Sarilumab	2023	Godolphin	PRISMA	Mortality	RCT	898	0.80 (0.61;1.04;0.09)	S: 0.123
Tocilizumab	2021	Avni	PRISMA	Mortality	RCT	6,481§	0.89 (0.82-0.96)	S: 0.064
Tocilizumab	2021	Hariyanto	PRISMA	Mortality	OBS, RCT	13,412§	0.54 (0.42;0.71;<0.00001)	S: 0.340
Tocilizumab	2021	Juul	PRISMA	Mortality	RCT	NA	1.03 (0.72;1.46;p=0.89)	No association
Tocilizumab	2021	Kow	-	Mortality	RCT	2,057	0.83 (0.66–1.05)	No association
Tocilizumab	2021	Mahroum	PRISMA	Mortality	OBS	3,657	0.74 (0.55;1.01;p=0.057)	No association
Tocilizumab	2021	Malgie	PRISMA	Mortality	OBS	1,358	0.27 (0.12;0.59)	M: 0.722
Tocilizumab	2021	Nugroho	PRISMA	Survival	OBS, RCT	2,112	1.65 (1.37;2.00)	S: 0.276
Tocilizumab	2021	Sarfraz	PRISMA	Mortality	OBS, RCT	2,120	0.42 (0.26;0.69;P=0.0005)	S: 0.478
Tocilizumab	2021	Selvaraj	PRISMA	Mortality	RCT	3,358	0.89 (0.80;0.98;p=0.02)	S: 0.064
Tocilizumab	2022	Boppana	PRISMA	Mortality	RCT	3,358	0.87 (0.73;1.03;p=0.11)	No association
Tocilizumab	2022	Gupta	PRISMA	Mortality	RCT	1,651	0.90 (0.76;1.07)	No association
Tocilizumab	2022	Lim	PRISMA	Mortality	OBS	2,035	0.52 (0.36;0.75)	S: 0.361
Tocilizumab	2022	Lim	PRISMA	Mortality	RCT	5,696	0.71 (0.55;0.92)	S: 0.189
Tocilizumab	2022	Mutua	PRISMA	Mortality	RCT	3,358	0.87 (0.73-1.04)	No association
Tocilizumab	2022	Piscoya	PRISMA	Mortality	OBS, RCT	4,689	0.89 (0.81;0.98;p=0.03)	S: 0.064
Tocilizumab	2022	Zhang	-	Mortality	RCT	3,358	0.89 (0.80;0.99)	S: 0.064
Tocilizumab	2023	Godolphin	PRISMA	Mortality	RCT	898	0.82 (0.71;0.95;0.008)	S: 0.109
Antimalarials								
Hydroxychloroquine & Chloroquine	2021	Qiu	PRISMA	Mortality	OBS, RCT	4,054	1.21 (0.88;1.68)	No association
Hydroxychloroquine & Chloroquine	2022	Di Stefano	PRISMA	Mortality	RCT	412	RD: -0,01 (-0.06;0.04)	No association
Hydroxychloroquine	2020	Talaie	PRISMA	Mortality	OBS, RCT	271	1.57 (1.03;2.39)	S: 0.249
Hydroxychloroquine	2020	Wang	PRISMA	Mortality	OBS, RCT	NA	1.08 (0.81;1.44)	No association
Hydroxychloroquine	2020	Das	PRISMA	TTVC	OBS	415	MD: 1.14 (-11.98;14.26;p=0.86)	No association
Hydroxychloroquine	2020	Das	PRISMA	TTVC	RCT	415	MD: 1.55 (-0.7;3.79;p=0.18)	No association
Hydroxychloroquine	2020	Mega	PRISMA	Mortality	OBS, RCT	1,311	1.26 (0.66;2.39)	No association
Hydroxychloroquine	2020	Shamshirian	PRISMA	Mortality	OBS, RCT	NA	0.86 (0.71;1.03)	No association
Hydroxychloroquine	2021	Zang	PRISMA	RT-PCR	OBS, RCT	441	1.11 (0.77;1.59;P=0.591)	No association
Hydroxychloroquine	2021	Bignardi	PRISMA	Mortality	RCT	7,629§	1.09 (0.98;1.20)	No association
Hydroxychloroquine	2021	Budhathoki	PRISMA	Mortality	OBS, RCT	388	1.16 (0.92-1.46)	No association
Hydroxychloroquine	2021	Cheng	-	Mortality	OBS, RCT	NA	1.01 (0.81;1.25)	No association
Hydroxychloroquine	2021	Choudhuri	PRISMA	Mortality	OBS, RCT	NA	1.003 (0.98;1.02)	No association
Hydroxychloroquine	2021	Di Castelnuovo	PRISMA	Mortality	OBS, RCT	NA	0.80 (0.69-0.93)	S: 0.123
Hydroxychloroquine	2021	Juul	PRISMA	Mortality	RCT	NA	1.09 (0.99;1.20;p=0.08)	No association
Hydroxychloroquine	2021	Kumar	PRISMA	Mortality	OBS, RCT	4,215	1.10 (1.00;1.20)	No association
Hydroxychloroquine	2021	Tanni	PRISMA	Mortality	RCT	714	RD: 0.00 (-0.01;0.02;p=0.98)	No association
Hydroxychloroquine	2022	De Moraes	PRISMA	Mortality	RCT	3,377	1.09 (0.99;1.19)	No association
Antivirals								
Antivirals	2020	Talaie	PRISMA	Mortality	OBS, RCT	NA	0.83 (0.55;1.24)	No association
Antivirals	2021	Qiu	PRISMA	Mortality	OBS, RCT	9,488	0.91 (0.80;1.04)	No association
Favipiravir	2020	Prakash	PRISMA	Clin. improvement	OBS, RCT	200	1.63 (1.07;2.48)	S: 0.269
Favipiravir	2022	Lan	PRISMA	Mortality	RCT	NA	0.99 (0.60;1.63)	No association
IFN-beta	2021	Kumar	PRISMA	Mortality	RCT	2,343	0.59 (0.91;1.12)	No association
IFN-beta	2021	Juul	PRISMA	Mortality	RCT	NA	0.75 (0.30;1.88;p=0.54)	No association
IFN-beta	2021	Nakhlband	PRISMA	Discharge rate	OBS, RCT	NA	3.05 (1.09;5.01)	M: 0.615
IFN	2022	Xue	-	Mortality	RCT	NA	0.416 (0.217;0.797)	S: 0.484
Lopinavir/ritonavir	2020	Bhattacharyya	PRISMA	Mortality	OBS, RCT	104	1.208 (0.563–2.592)	No association
Lopinavir/ritonavir	2020	Verdugo	PRISMA	Mortality	RCT	133	0.77 (0.45;1.30)	No association
Lopinavir/ritonavir	2020	Wang	PRISMA	Mortality	OBS, RCT	NA	0.68 (0.39;1.19)	No association
Lopinavir/ritonavir	2021	Juul	PRISMA	Mortality	RCT	NA	1.01 (0.92;1.12;p=0.77)	No association
Remdesivir	2020	Prasad	PRISMA	Mortality	OBS, RCT	696	0.74 (0.40;1.37)	No association
Remdesivir	2020	Piscoya	PRISMA	Mortality	RCT	691	0.71 (0.39;1.28)	No association
Remdesivir	2020	Verdugo	PRISMA	Mortality	RCT	1,080	0.70 (0.46;1.05)	No association
Remdesivir	2020	Wang	PRISMA	Mortality	OBS, RCT	NA	0.64 (0.44;0.94)	S: 0.246
Remdesivir	2021	Al-Abdouh	PRISMA	Mortality	RCT	3,818	RD: -0.01 (-0.03;0.01)	No association
Remdesivir	2021	Enoki	-	Mortality	RCT	1,080	0.67 (0.37;1.19)	No association
Remdesivir	2021	Gholamhoseini	PRISMA	Mortality	OBS, RCT	NA	0.769 (0.563;1.050;p=0.098)	No association
Remdesivir	2021	Juul	PRISMA	Mortality	RCT	3812	0.93 (0.82;1.07;p=0.31)	No association
Remdesivir	2021	Okoli	PRISMA	Mortality	RCT	7,143	0.94 (0.82;1.07)	No association
Remdesivir	2021	Rezagholizadeh	PRISMA	28-day recovery	RCT	NA	1.09 (1.04;1,15)	S: 0.048
Remdesivir	2022	Tanni	PRISMA	Mortality	RCT	4,083	RD: -0.01 (-0.02;0.01)	No association
Remdesivir	2022	Tanni	PRISMA	Mortality	OBS	1,639	RD: -0.02 (-0.07;0.03)	No association
Umifenovir	2021	Amani	PRISMA	RT-PCR	OBS, RCT	108	1.10 (0.96;1.25)	No association

* By convention, for Cohen's "d" of 0-0.4; 0.5-0.7 and ≥ 0.8 are considered small (S), medium (M) and large (L) effect sizes respectively (Chen, 2010). Cohen's d was calculated using the tool available at the following URL: https://www.escal.site.

§Total number of patients (experimental and control groups).

IFN: interferon; MD: mean difference; NA: not available; OBS: observational studies; RCT: ramdomized clinical trials; RD: risk difference; RT-PCR: RT-PCR negative conversion; TTVC: time to virological cure (days).